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Original Article

Hematological Alterations on Sub-acute Exposure to Flubendiamide in Sprague Dawley Rats

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ABSTRACT

Background: Pesticide poisoning is a common occurrence around the world. Pesticides can act on various body systems resulting in toxicity. Flubendiamide is a new generation pesticide, reported to have better activity against Lepidopteran insects. The present study was carried out with an objective to analyze the effects of flubendiamide sub-acute exposure on hematology of rats. **Materials and Methods:** Male and female Sprague Dawley (SD) rats (9–11 weeks) were divided into five groups with six animals in each group. First group served as control, while the rest were exposed to ascending oral doses of flubendiamide (125, 250, 500 and 1000 mg/kg) for 28 days. After the trial period, blood was collected in heparinized vials and analyzed using Siemens ADVIA 2120®autoanalyzer. Various erythrocytic, platelet and leukocyte parameters were measured and analyzed using statistical tests by one-way analysis of variance (ANOVA) and *t*-test using Statistical Package for Social Sciences (SPSS)® 20 software. **Results:** After processing the data through statistical analysis, it was observed that the effect of flubendiamide exposure on female rats was negligible. The only significant change observed in the female rats was that in total erythrocytic count, while rest of the parameters showed non-significant bidirectional changes. In males, many parameters viz., total leukocyte count (TLC), total erythrocyte count (TEC), packed cell volume (PCV), mean corpuscular volume (MCV), platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), hemoglobin distribution width (HDW), large platelets (LPT) and plateletcrit (PCT) expressed significant difference when compared to control. **Conclusion:** Many of the changes were dose independent, but sex specific. This lead to the hypothesis that saturation toxicokinetics might be one of the reasons for this varied response, which can only be evaluated after further testing.

Key words: Erythrocytic indices, flubendiamide, hemoautoanalyser, platelet, sub-acute toxicity

INTRODUCTION

Pesticides and fertilizers form an integral part of the agriculture system in India. Due to the increasing demand in food production, there is an increase in pesticide use in intensive agrarian states such as Punjab, Haryana, Andhra Pradesh, Gujarat etc.[1] Pesticide toxicity in animals has become a matter of serious concern in the last few decades due to rapid industrial expansion and adoption of intensive farming practices in India.[2]

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Flubendiamide (N2-[1,1-dimethyl-2-(methylsulfonyl) ethyl]-3-iodo-N1-[2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl) ethyl] phenyl]-1,2-benzene dicarboxamide) belongs to phthalic acid diamide group with potent, broad-spectrum activity against the insects of

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order Lepidoptera.[3] The novelty of this compound lies in its selectivity to activate insect ryanodine receptors (RyRs) present on neurons and skeletal muscle; thereby leading to massive intracellular release of calcium ions.[4] This target is attractive for insecticides with no cross-resistance to other known modes of action.[5] The diamides have been classified under new group (28: Ryanodine receptor modulators) by the Insecticide Resistance Action Committee (IRAC, www.irac-online.org). Flubendiamide was registered in India in the year 2007 under the trademark Fame.[6] Major uses of flubendiamide as per the guidance document of the Government of India include application in pigeon pea, black gram, chilli, tomato, cabbage, cotton and rice crops.[7]

The reported median lethal dose (LD_{50}) was more than 2,000 mg/kg for both male and female rats indicating that the pesticide is safe even after accidental consumption. Females were reported to be highly sensitive to flubendiamide when compared to males.[8] Though, no mammalian toxicity has been published so far, there were reports of flubendiamide poisoning in buffaloes upon consumption of fodder recently sprayed with the pesticide (unpublished data). Acute toxicity of agricultural pesticides (flubendiamide, endosulfan, and spirotetramat) to embryo, larval, and juvenile stages of African catfish, *Clarias gariepinus*, has been carried out recently. It was found that flubendiamide was toxic with LC_{50} 48 h at 2 ppm (2 µg/mL). All stages of fish life, that is, egg, larva, juvenile, and adults were susceptible to flubendiamide.[9] Chronic studies of flubendiamide exposure in rodents have been reported to have a negative impact on growth.[10] Due to the scarcity of data on effect of flubendiamide exposure on hematology, the present study was planned with an objective to test the pesticide sub-acute exposure on hematology in Sprague Dawley (SD) rats.

MATERIALS AND METHODS

Thirty male and female SD rats of 9–11 weeks of age were used in the present study. Rats were obtained from National Institute of Pharmaceutical Education and Research, Mohali, India. They were maintained under optimal conditions of 12:12 h light-dark cycle, *ad libitum* feed (Rat Pellet Feed, Ashirwad Industries®, Chandigarh, India), and water supply. Study was carried out after obtaining permission from Institutional Animal Ethics Committee (IAEC; Lr. No. VMC/14/2413-43 dated 10.06.2014). After acclimatization for a week, rats were dosed orally with flubendiamide (technical grade) for 28 days. Rats were divided into five groups with three male and three female rats in each group with a coefficient of variation of less than 10% for body weight. Group I acted as control and received only vehicle (0.4% Tween 80 (Merck, India)), whereas Groups II, III, IV and V received flubendiamide at a dose rate of 125, 250, 500 and 1,000 mg/kg body weight. Pesticide was prepared as suspension and the concentrations were prepared so that the dosing volume in each group was between 1–2 ml/100 g body weight as per the Organization for Economic Co-operation and Development (OECD) guidelines. After completion of the trial, whole blood samples were collected using heparin sodium (at 0.5–2 IU per ml of blood) as anticoagulant. Sampling period covering all animals was completed in 2-h duration (7.00 A. M.–9.00 A. M.). Samples were instantly analyzed for various hematological parameters using Siemens ADVIA 2120® hemoautoanalyzer following manufacturer's instructions. Hematological parameters analyzed include total leukocyte count (TLC), total erythrocyte count (TEC), hemoglobin (Hb), packed cell volume (PCV), total platelet count (TPC), mean platelet volume (MPV), red cell hemoglobin concentration mean (CHCM), cellular hemoglobin concentration (CM), platelet distribution width (PDW), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), hemoglobin distribution width (HDW), plateletcrit (PCT), mean platelet component (MPC) and large platelets (LPTs). Table 1 describes in detail the parameters measured along with units giving a reference value of hematological indices in male and female SD rats of 13 weeks of age.[11] All the results have been analyzed using Statistical Package for Social Sciences® version 20 through one-way analysis of variance followed by Tukey's post-hoc test and unpaired *t*-test to compare between male and female rats. All the values are expressed as mean ± standard error (SE).

RESULTS

Results of the study are presented in Tables 2 and 3. In female rats, significant ($P < 0.05$) difference in TEC was observed. There was an overall decrease in the RBC counts with respect to dose rate. Rest of the parameters exhibited non-significant decrease. In males, parameters viz., WBC, RBC, PCV, MCV, PLT, MPV, PDW, HDW, LPT and PCT expressed significant ($P < 0.05$) difference. There was significant ($P < 0.05$) decrease in WBC, LPT, PCT, PDW, MPV and PCs; while significant increase was observed in parameters viz., RBC, PCV and HDW. The results in the present study indicated a bidirectional response in some parameters, wherein there was increase/decrease till exposure of 500 or sometimes 250 mg/kg; while any further increase in dose resulted in returning of the values comparable to control and seldom beyond that of control. Significant differences were observed between male and female rats of the same group for parameters viz., RBC, Hb, PCV, RDW, MCHC, CHCM, CH and LPTs. Of these parameters, sex-dependent differences were consistent across most groups in Hb and PCV. There was dose-dependent increase in RBC, Hb, and PCV in males; whereas dose-dependent decrease was observed in female rats. MCH, MCHC and RDW showed a vice versa response

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Table 1: Reference values along with brief description for various hematological indices in Sprague Dawley rats

Parameter	Description (formulae if any)	Unit	SD rats (13 weeks)[11]	
			Males	Females
Red blood cell	Numbers - directly measured	10^6 cells/µL	9.1±0.5	8.2±0.4
PCV (hematocrit)	Calculated volume of RBC in blood=(RBC*MCV)/10	%	48±2.5	44.3±2.1
Hemoglobin	Measured hemoglobin in blood	g/dL	16.2±7	15.2±7
Cellular hemoglobin	Mean of cellular hemoglobin histogram	pg		
Mean corpuscular volume	Calculated average size of RBC -mean of volume histogram	fL	52.8±3	53.8±2.1
Red cell distribution width	Coefficient of variation of size	%	–	–
Cell hemoglobin concentration mean	Mean of RBC hemoglobin concentration histogram	g/dL	–	–
Hemoglobin distribution width	Standard deviation of RBC hemoglobin histogram	g/dL	–	–
Mean corpuscular hemoglobin	Amount of hemoglobin per cell=(Hb/RBC)*10	pg	17.9±0.8	18.4±0.6
Mean corpuscular hemoglobin concentration	Concentration of hemoglobin per cell=(Hb/(RBC*MCV))*1,000	g/dL	33.9±11	34.3±10
Leukocytes	Numbers - directly measured	10^3 cells/µL	10.8±2.4	7.8±2.4
Platelet distribution width	Indicative of the size of platelets	%	–	–
Platelet count	Numbers - directly measured	10^3/µL	959±136.2	1037.9±140.9
Mean platelet volume	Equivalent to MCV -mean of platelet volume histogram	fL	4.4±0.2	4±0.3
Plateletcrit	Volume of circulating platelets	%	–	–
Mean platelet component	Concentration of component in platelets	g/dL	–	–
Large platelets	Cells with volume greater than 20fL	10^3/µL	–	–

RBC = Red blood cell, MCV = Mean corpuscular volume, Hb = Hemoglobin

Table 2: Hematological parameters (RBC, Hb, PCV (HCT), CHCM, CM, MCV, MCH, MCHC, RDW and HDW) measured after sub-acute exposure to flubendiamide in SD rats

Parameter	Group	Male	Female	Parameter	Group	Male	Female
HDW	I	2.12±0.11^a	2.32±0.24	MCH	I	21.05±0.55	20.67±0.59
	II	3.12±0.22^b	2.53±0.24		II	19.62±1.402	19.6±0.4
	III	2.38±0.17^{ab}	2.85±0.2		III	18.97±0.33	20.27±0.38
	IV	2.43±0.33^{ab}	2.06±0.09		IV	18.97±0.067	19.87±0.23
	V	2.23±0.04^{ab}	2.4±0.27		V	18.33±0.22	19.63±1.01
RBC	I	6.99±0.50^a	8±0.14^b	MCHC	I	36.7±0.06	36.9±0.6
	II	7.99±0.57^{ab}	7.56±0.06^a		II	36.29±2.59	35.8±0.4
	III	7.34±0.28^{ab}	7.85±0.13^b		III	35.2±0.17	36.4±0.17**
	IV	8.36±0.02^{ab}*	7.76±0.1^b		IV	34.3±0.1	35±0.21
	V	8.98±0.24^b	6.84±0.33^a		V	34.27±0.19	35.2±1.11
Hb	I	14.65±0.66	16.53±0.65	CHCM	I	27.6±2.08	32.17±0.43
	II	15.45±1.11	14.85±0.43		II	31.52±2.25	31.75±0.32
	III	13.93±0.32	15.93±0.18*		III	31.1±0.31	32.07±0.19
	IV	15.87±0.03**	15.4±0.06		IV	30.63±0.17	31.5±0.12*
	V	16.43±0.24	13.5±1.34		V	31.3±0.1	31.97±0.59
PCV (HCT)	I	39.9±1.85^a	44.83±1.37	CH	I	15.7±0.81	18±0.5
	II	43.31±3.1^{ab}	41.4±0.69		II	17.08±1.22	17.35±0.32
	III	39.47±0.83^a	43.8±0.42*		III	16.7±0.44	17.9±0.29
	IV	46.23±0.19^{ab}*	44.03±0.43		IV	16.9±0.1	17.83±0.22*
	V	48.03±0.94^b	38.23±2.74		V	16.67±0.19	17.77±0.72
MCV	I	57.4±1.44	55.93±0.88	RDW	I	14.4±0.35	12.67±1.52
	II	55±3.93	54.75±0.49		II	17.59±1.26*	12.25±0.66
	III	53.87±1.102	55.77±0.79		III	13.97±1.11	14.67±1.04
	IV	55.33±0.29	56.77±0.64		IV	14.07±1.7	10.67±0.12
	V	53.47±0.44	55.7±1.33		V	12.63±0.2	11.93±1.02

* and ** indicate significant difference at $P<0.05$ and $P<0.01$, respectively when compared between sex and within group. Values (mean±SE) with different superscripts within sex differ significantly ($P<0.05$) between groups. RBC = Red blood cell, Hb = Hemoglobin, PCV = Packed cell volume, HCT = Hematocrit, CHCM = Red cell hemoglobin concentration mean, CM = Cellular hemoglobin concentration, MCV = Mean corpuscular volume, MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration, RDW = Red cell distribution width, HDW = Hemoglobin distribution width

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Table 3: Hematological parameters (WBC, PCT, MPC, LPT, PLT, MPV and PDW) measured after sub-acute exposure to flubendiamide in SD

Parameter	Group	Male	Female	Parameter	Group	Male	Female
MPV	I	18.35±4.01^{b}	9.03±1.67	PCT	I	2.63±0.92^{b}	0.49±0.11
	II	7.12±0.51^{a}	7.25±0.32		II	0.58±0.04^{a}	0.68±0.03
	III	11.93±3.23^{ab}	7.53±0.41		III	0.38±0.13^{a}	0.53±0.09
	IV	7.27±0.29^{a}	7.63±0.088		IV	0.68±0.02^{a}	0.68±0.03
	V	7.23±0.15^{a}	9.18±0.32*		V	0.67±0.01^{a}	0.56±0.24
PDW	I	106.2±10.16^{c}	84.63±9.34	MPC	I	21.7±0.75	22.33±1.03
	II	55.21±3.95^{a}	74.85±6.09		II	23.89±1.71	23.05±0.55
	III	92.67±3.99^{bc}	73.73±10.25		III	20.2±1.65	22.37±0.03
	IV	73.3±6.08^{ab}	67.8±2.74		IV	23.17±0.33	21.83±0.03
	V	81.17±3.44^{abc}	95.67±2.04		V	24.4±0.41	22.33±0.94
PLT	I	1287±219.97^{b}	615±188.51	LPT	I	384.5±161.37^{b}	23±9.65
	II	831.63±59.43^{ab}	946±75.06		II	5.08±0.36^{a}	15.5±4.33
	III	416.67±206.99^{a}	724±144.97		III	25.67±1.45^{a}*	11.67±3.67
	IV	943±8.51^{ab}	900±35.57		IV	15.67±4.37^{a}	16±1.5
	V	926±11^{ab}	617.67±263.52		V	20.67±3.28^{a}	43.33±21.37
WBC	I	18.41±4.29^{b}	13.31±0.40				
	II	15.55±1.11^{ab}	13.9±1.89				
	III	6.85±1.45^{a}	12.9±0.18				
	IV	11.62±0.83^{ab}	11.69±0.64				
	V	13.67±0.12^{ab}	15.29±2.65				

*Indicates significant difference at (P<0.05) when compared between sex and within group. Values (mean±SE) with different superscripts within sex differ significantly (P<0.05) between groups. WBC = White blood cell, PCT = Plateletcrit, MPC = Mean platelet component, LPT = Large platelet, PLT = Platelet, MPV = Mean platelet volume, PDW = Platelet distribution width

upon increase in exposure dose rate. In case of platelet parameters, similar response was observed in PC, PDW as well as LPTs. There was significantly high number of LPTs in control group of males. Results indicated a significant effect of hematology parameters, especially in males.

DISCUSSION

Flubendiamide stabilizes insect RyRs in open state, evoking massive calcium release from intracellular stores leading to sustained muscle contraction followed by death. However, flubendiamide has a high affinity for insect RyRs.[12] In order to test if there are any effects on hematopoiesis, which may either be related or unrelated to the pesticides mechanism of insecticidal activity, the present study was carried out in male and female SD rats. Alterations in hematological parameters were analyzed using unpaired t-test for sex-dependent changes, whereas dose-dependent effects were analyzed using one-way analysis of variance (ANOVA).

Any mutations in the protein structure of RyRs would have led to adverse effects in animals; especially domesticated herbivores that are being maintained specially on green fodder which might have resulted in isolated events of flubendiamide toxicity as already mentioned (unpublished data). These events were characterized by high body temperature due to persistent muscular contraction similar to the pesticides mechanism of action in insects. Alterations in the values of erythrocytic parameters would indicate effect on the mechanism of the genesis or termination of erythrocytes. In concurrence to the previous reports, flubendiamide resulted in marginal alterations in hematological parameters.[13] Platelets play an important role in coagulation and any deficit in the structure, numbers and stability would lead to bleeding or thrombic disorders; ultimately resulting in death. White blood cells play an important role in defense against invading bacteria, virus, fungi, etc., Any alteration in their numbers would result in deregulation of immune status. Due to the major role of calcium in most of the cellular activities from adenosine triphosphate (ATP) synthesis to regulation of hematopoiesis, any compound that alters its levels in body would affect any of these parameters.[14]

Great variation in the number of leukocytes due to excitable nature of rats has been previously reported. Platelets have played an important role in assessing the risk of cardiovascular health using parameters such as PDW for thrombocytosis[15] and MPV for overall vascular mortality, ischemic heart disease,[16] myocardial infarction, unstable angina, etc.[17] The temporal increase of MPV during storage of blood samples is usually attributed to platelet activation as it is combined with a decrease in platelet component concentration (MPC).[18] However, platelet degranulation as well as simple platelet swelling can be the cause of decrease in MPC. The high numbers of LPTs in the control group might be due to sampling

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time, as the sacrifice and sampling started with the control group followed by others resulting in a difference between sampling and analyzing time (more than 2 h) of platelets. It has been reported that upon storage, platelets get activated leading to increase in their volume resulting in LPTs.[18]

After analysis of differences between male and female rats among all the parameters analyzed, negligible differences have been observed. Most of the sex-dependent differences were observed in Group IV, especially in erythrocytic parameters, which might indicate sensitivity of males more than females for the pesticide used, which is in contrary to the previous reports.[8]

Interestingly, an increase in dose rate beyond 500 mg/kg exhibited reversal of response in multiple parameters as can be seen in Tables 2 and 3. The reason for this type of response might be due to saturation in the toxicokinetics of pesticide at higher dose, thereby resulting in zero order kinetics in absorption phase. Though non-significant, results indicate a stimuluslike effect on erythrocytic indices in males; but inhibitory in females basing on the changes in parameters in Groups I–V. Reason for these effects should further be verified using immunological and molecular methods to detect the mechanism for the cause as well as variability across different exposure levels.

All the parameters were in the range of reported normal values of SD rats, independent of dose rate rendering it difficult to interpret the changes in the present study. In order to be accurate in estimation, the adverse effects of the present study, a 0-day sample should have been analyzed, but this would have resulted in additional stress in animals and is not recommended. It has also been reported that the site of sample (blood) collection plays a vital role in the resulting parameters.[19]

From the present study, hemotoxicity have been observed in Group IV (500 mg/kg), wherein significant decrease and increase in erythrocyte and platelet parameters, respectively, have been observed. There were no previous reports indicating effect of flubendiamide on platelets if any. It can be concluded from the present study that flubendiamide has resulted in negligible toxicity leading to variable effects on the hematological parameters.

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REFERENCES

1. Tiwana NS, Jerath N, Singh G, Singh R. Pesticide pollution in Punjab: A review. Asian J Water Environ Pollut 2007;6:89-96.
2. INSA. Hazardous metals and minerals pollution in India: Source, toxicity and management: A position paper. Indian National Science Academy, New Delhi; 2011.
3. Das SK, Mukherjee I. Effect of light and pH on persistence of flubendiamide. Bull Environ Contam Toxicol 2011;87:292-6.
4. Lahm GP, Cordova D, Barry JD. New and selective ryanodine receptor activators for insect control. Bioorg Med Chem 2009;17:4127-33.
5. Sattelle DB, Cordova D, Cheek TR. Insect ryanodine receptors: Molecular targets for novel pest control chemicals. Invert Neurosci 2008;8:107-19.
6. Legocki J, Połeć I, Żelechowski K. Contemporary trends in development of active substances possessing the pesticidal properties: Ryanodine-receptor targeting insecticides. Pestic 2008;3-4:15-26.
7. Ministry of Agriculture. Major uses of pesticides. Guidance document issued by Department of Agriculture and Cooperation, Directorate of Plant Protection, Quarantine and Storage, Central Insecticides Board and Registration Committee, Government of India, 2012.
8. APVMA. Public release summary on evaluation of the new active flubendiamide in the products BELT 480 SC insecticides and BELT 240 WG insecticide. Australian Pesticide and Veterinary Medicines Authority, Canberra, Australia; 2009.
9. Agbohessi PT, Imorou Toko I, Houndji A, Gillardin V, Mandiki SN, Kestemont P. Acute toxicity of agricultural pesticides to embryo-larval and juvenile African catfish *Clarias gariepinus*. Arch Environ Contam Toxicol 2013;64:692-700.
10. Justus K, Motoba K, Reiver H. Metabolism of flubendiamide in animals and plants. Plant Protection Nachrichtern Bayer 2007;60:141-66.
11. Petterino C, Argentino-Storino A. Clinical chemistry and haematology historical data in control Sprague-Dawley rats from pre-clinical toxicity studies. Exp Toxicol Pathol 2006;57:213-9.
12. Ebbinghaus-Kintscher U, Luemmen P, Lobitz N, Schulte T, Funke C, Fischer R, *et al*. Phthalic acid diamides activate ryanodine-sensitive Ca^{2+}release channels in insects. Cell Calcium 2006;39:21-33.
13. Ranjan A, Dumka VK, Singh ND. Effect of flubendiamide, lead and their combined exposure on erythrocytic indices in water buffalo calves. Bull Environ Contam Toxicol 2014;92:410-4.
14. Parades-Gamero EJ, Barbosa CM, Ferreira AT. Calcium signalling as a regulator of haematopoiesis. Front Biosci (Elite Ed) 2012;4:1375-84.
15. Osselaer JC, Jamart J, Scheiff JM. Platelet distribution width for differential diagnosis of thrombocytosis. Clin Chem 1997;43:1072-6.
16. Slavka G, Perkmann T, Haslacher H, Greisenegger S, Marsik C, Wagner OF, *et al*. Mean platelet volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease. Arterioscler Thromb Vasc Biol 2011;31:1215-8.
17. Yaghoubi A, Golmohamadi Z, Alizadehasl A, Azarfarin R. Role of platelet parameters and haematological indices in myocardial infarction and unstable angina. J Pak Med Assoc 2013;63:1133-7.

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18. Van Cott EM, Fletcher SR, Kratz A. Effects of the blood-collection tube material and long-term storage on platelet activation parameters on the ADVIA 120/2120 hematology system. Lab Hematol 2005;11:71-5.
19. Seibel J, Bodie K, Weber S, Bury D, Kron M, Blaich G. Comparison of haematology, coagulation and clinical chemistry parameters in blood samples from the sublingual vein and vena cava in Sprague–Dawley rats. Lab Anim 2010;44:344-51.

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